Proliferation of Novel Synthetic Opioids in Postmortem Investigations After Core-Structure Scheduling for Fentanyl-Related Substances

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Abstract: New generations of novel synthetic opioids (NSOs) have emerged to fill a void in the illicit drug markets left by the decline in popularity of fentanyl analogs subsequent to core-structure scheduling of fentanyl-related substances in the United States and China. These new opioids include members of the 2-benzyl benzimidazole (eg, isotonitazene, metonitazene, *N*-pyrrolidino etonitazene, protonitazene, etodesnitazene), benzimidazolone (eg, brorphine), and cinnamylpiperazine (eg, AP-238, 2-methyl AP-237) subclasses. Novel synthetic opioids continue to be detected in opioid-related fatal overdoses, demonstrating the harms associated with exposure to these drugs. Between January 2020 and December 2021, 384 casework blood samples were reported by our laboratory to contain 1 or more of the prior listed 8 NSOs. Isotonitazene (n = 144), metonitazene (n = 122), and brorphine (n = 91) were the 3 most prevalent substances, with positivity for isotonitazene and brorphine peaking just before the announcement of emergency scheduling. These NSOs have been documented as significant drivers of drug mortality, and this case series described here highlights the challenges medical examiners and coroners face in staying current with emerging drugs. Challenges include regional differences, rapid turnover, short lifecycles, variable toxicology testing, and difficulty in assessing individual drug toxicity in polydrug cases.

Key Words: opioids, postmortem, toxicology, NSO, NPS, forensic

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Novel synthetic opioids (NSOs) have intensified the on-going opioid crisis since the appearance of illicit fentanyl in the United States (US) heroin supply in 2008.[1–16] The US Centers for Disease Control and Prevention estimate that there will be more than 100,000 opioid deaths in 2021.[17] Illicit drug manufacturers have continued to introduce a variety of novel opioid agonist structural classes with varying potencies, which have been contributory and/or causal agents in nonfatal and fatal overdoses.[18–38] Between 2015 and 2018, most NSO-classified novel psychoactive substances (NPSs) infiltrating the illicit drug market were fentanyl analogs, such as 2-furanylfentanyl, carfentanil, acrylfentanyl, methoxyacetylfentanyl, and cyclopropylfentanyl.[39–60] Nonfentanyl NSOs, such as MT-45, AH-7921, and U-47700, also appeared during that time but in comparatively smaller numbers.[45,61–67] Over the last 10 years, the market for NSOs has further diversified. Between 2009 and 2019, the number of NPS drugs with opioid effects reported to the United Nations Office on Drugs and Crime Early Warning Advisory rose from 1 to 55.[68]

In response to the rise in NSOs and the growing opioid crisis, a series of domestic and international controls have been implemented. In 2018, the 61st Session of the United Nations Commission on Narcotic Drugs adopted a resolution to enhance and strengthen international and regional cooperation to address threats posed by nonmedical use of synthetic opioids.[69] The same year, the United Nations Office on Drugs and Crime launched a plan for a coordinated international response among its member states toward the opioid crisis. Between 2018 and 2020, the United Nations Commission on Narcotic Drugs scheduled 12 individual fentanyl analogs under the 1961 Convention.[68] As a different approach after similar individual scheduling actions, the US Drug Enforcement Administration (DEA) imposed a temporary classwide scheduling ban on fentanyl-related substances in February 2018—a novel policy approach.[70] This action focused on the core structure of fentanyl and listed covered chemical modifications for a broader measure of scheduling compared with listing individual compounds; this measure effectively banned a large swath of fentanyl analogs. This has been extended several times, but it scheduled to expire in 2022.[71] In 2019, China then followed suit with similar action, in addition to a ban on fentanyl precursors N-phenethyl-4-piperidinone and 4-anilino-N-phenethylpiperidine.[72] On the whole, these international policy changes resulted in a marked decline in fentanyl analogs beginning in mid to late 2018, although fentanyl itself continues to be the major player among opioid-involved deaths.[73]

Although these core structure scheduling actions may have curbed the spread of fentanyl analogs, a subsequent shift toward novel and varied chemical classes of drugs with opioid activity has resulted. Today, most NSOs are seemingly pirated from pharmaceutical patents, literature, and research.[74] These include substances of the 2-benzyl benzimidazole, benzimidazolone, and cinnamylpiperazine subclasses.[68] In addition, there have been a number of reports of additional substances with opioid effects, including piperidylthiambutene, 2-fluoro viminol, and diphenpipenol.[75–77]

The 2-benzyl benzimidazole subclass (or nitazenes) is a group of drugs originally investigated for therapeutic analgesic properties in the 1950s. Etonitazene was the prototypical substance that was subsequently internationally controlled because of its high potency compared with other opioids, such as fentanyl.[78–80] It was suggested in 2012 that nitazene analogs could be misused leading to harm due to the abuse liability of etonitazene.[81] This prediction proved true in 2019 when isotonitazene, first developed at the same time as etonitazene and with potency and efficacy comparable with or greater than that of fentanyl, emerged on the illicit opioid market.[82–87] Isotonitazene was quickly linked to fatal overdoses and was subsequently emergency scheduled by the DEA in August 2020.[83,84,88–92] Additional nitazene analogs have followed suit and infiltrated the NSO supply to varying degrees; these include metonitazene, *N*-pyrrolidino etonitazene (also

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referred to as etonitazepyne), etodesnitazene, protonitazene, and metodesnitazene.[93–100] Of these additional nitazene analogs, most are reported to exhibit analgesic potency in animal models greater than fentanyl, with *N*-pyrrolidino etonitazene being the most potent, followed by protonitazene and metonitazene; etodesnitazene and metodesnitazene are reported to be less potent than fentanyl.[101] In December 2021, metonitazene was the 2-benzyl benzimidazole with the highest prevalence in toxicological casework.

Brorphine, which was first reported in Europe in early 2020, quickly became the newest replacement on the US NSO market following DEA scheduling of isotonitazene and its subsequent rapid decline in positivity.[102,103] Brorphine is a substituted piperidine-based benzimidazolone, retaining some structural similarity to fentanyl; however, it falls outside the scope of the DEA's core structure scheduling of fentanyl-related substances. This NSO subclass was first developed as central nervous system depressants with morphine-like analgesic activity.[104] In vitro studies demonstrated that brorphine is a full μ opioid receptor agonist with a higher potency compared with morphine.[103,105] After detection and reporting of brorphine in postmortem cases in the US in 2020, the DEA again moved with intent to schedule the new NSO in December 2020, taking effect in March 2021.[102,106–108] Not long after this notice, positivity for brorphine in postmortem casework began to fall rapidly, and metonitazene emerged as the newest replacement. Metonitazene popularity generally increased throughout 2021, resulting in another shift that drug surveillance stakeholders have to account for.[109,110] *N*-pyrrolidino etonitazene also emerged and gained popularity in late 2021, therefore broadening the diversity of the nitazene subclass detected in postmortem casework.[110]

In addition to 2-benzyl benzimidazole and benzimidazolone, 2 additional drugs of the cinnamylpiperazine subclass have emerged on the illicit drug market. 2-Methyl AP-237 and AP-238 are structurally related to AP-237 (also known as bucinnazine), the prototypical opioid of this subclass. AP-237 was originally approved in China in the 1960s for pain management in cancer patients, whereas 2-methyl AP-237 was patented in the 1980s.[111–113] 2-Methyl AP-237 is estimated to have 68 to 156 times less analgesic potency than fentanyl (ie, equivalent to, or less potent that morphine), which may account for a lack of popularity in the drug market thus far.[114] Pharmacological data for AP-238 demonstrated that is more potent than 2-methyl AP-237 yet approximately 11 times less potent compared with fentanyl.[115]

Emerging NSOs pose significant risks to public health and safety due to varying potencies (often greater than fentanyl), ease of infiltration into the recreational opioid supply, and increasing reports of adverse events and harm. Like traditional opioid agonists (eg, fentanyl), the use of NSOs can result in sedation, euphoria, and respiratory depression that can progress to coma and death. The infiltration of NSOs into the drug supply often occurs in one of 3 manners: (1) as a standalone drug product purchased from a gray market, often online vendor (eg, white powder containing only 2-methyl AP-237), (2) as a full substitution of an opioid drug supply with the NSO (eg, isotonitazene sold as "heroin" but the powder is absent other opioids), or (3) as a mixture with fentanyl or heroin distributed in the broader supply (eg, brorphine present with fentanyl in the "heroin" supply).[68,86,116] When NSOs are mixed with or substituted for routinely encountered opioid, such as fentanyl and/or heroin, users are likely to be ingesting these substances, which can lead to increased likelihood of adverse reactions due to unknown potency of the actual drug administered. The circumstances and factors involving an NSO-related adverse event or death are different and must be treated as such, reinforcing the importance of thorough scene investigation and communication between drug chemists, toxicologists, and forensic pathologists.

METHODS

Broad-spectrum toxicology testing of samples from medicolegal death investigations and driving under the influence (DUI) investigations was conducted via a comprehensive drug screening protocol with analysis by high-resolution mass spectrometry. Biological samples (eg, blood) were analyzed by liquid chromatography time-of-flight mass spectrometry (LC-TOF-MS) using an Agilent Technologies 6230 LC-TOF-MS (Santa Clara, CA). This assay was fully validated to detect more than 325 recreational, therapeutic, and emerging synthetic drugs, as well as a subpanel dedicated to NPS, as discussed in previous work.[90] Between 2019 and 2021, isotonitazene, brorphine, metonitazene, *N*-pyrrolidino etonitazene, protonitazene, etodesnitazene, 2-methyl AP-237, and AP-238 (structures shown in Fig. 1) were identified by reprocessing the TOF data files against a secondary library.

Data processing for emerging NSOs was performed using a targeted approach through Agilent MassHunter Qualitative Analysis Workflows (B.08.00) and an in-house NPS library database. The library consisted of analyte name, formula, exact protonated mass, and retention time; these characteristics are indicated in Table 1. Presumptive identifications were recorded for data files that met lenient criteria for mass error (<20 ppm) and retention time error (<0.35 minutes) to account for retention drift due to the use of 4 different instruments of the same make/model running the same method. Processing results were filtered based on software scoring to assist with identifications. Peak area response was reviewed for appropriate chromatographic characteristics and compared against a set of peak intensity thresholds from a previously analyzed cutoff calibrator. Peak intensity in the sample was required to meet or exceed the intensity of this threshold to recommend confirmation testing by a toxicologist. The cutoff calibrator was selected to represent a concentration that could be analytically confirmed.

All positive findings were reviewed by a toxicologist and approved for subsequent quantitative confirmatory analysis. Because of the low number of samples included in the survey, quantitative confirmations were conducted using a standard addition approach for the quantitation of NPS in biological matrices due to their rapid emergence and decreased time for development of fully validated assays.[117–120] Cases that were screened in other laboratories were analyzed directly by the standard addition method without the high-resolution mass spectrometry screen.

For quantitation, samples were prepared using a 3-point standard addition protocol that has previously been described.[118] Four aliquots (0.2) mL of each unknown sample were prepared: 1 aliquot deemed the "blank" was unfortified and the 3 remaining aliquots per case were fortified at increasing concentrations of target analyte. Internal standard was added to all samples. Samples were prepared using a liquid-liquid extraction (LLE). Instrumental analysis was performed by liquid chromatography triple quadrupole tandem mass spectrometry (LC-QQQ-MS) on a Waters Xevo TQ-XS coupled to a Waters Acquity UPLC (Milford, Mass). The concentration of NSO in the sample was determined through back calculation of the x-intercept using a linear fit between up-spike concentration and resulting analyte-internal standard peak area ratio calculated in Microsoft Excel (Richmond, Wash). Acceptance criteria for the standard addition required a correlation coefficient of $R^2 > 0.98$, as well as criteria typically required for confirmation and identification (eg, correct retention time, within ion ratio limits, etc).

RESULTS

In total, 384 blood samples were submitted and confirmed for the presence of 1 or more specified NSOs. Cases were reported

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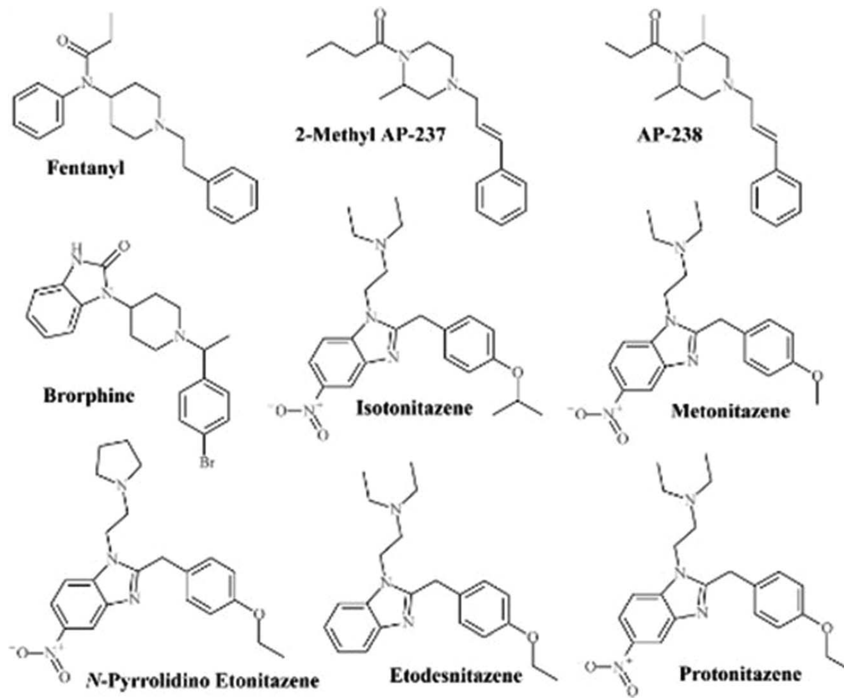

FIGURE 1. Chemical structures of novel synthetic opioids.

between January 2020 and December 2021 (collection dates for 7 studied specimens were before 2020); cases reported herein complement previously reported case series by the authors.[90,107,109,115,121] Table 2 shows the number of detections for each NSO, as well as mean, median, and range of quantitative results.

Of the 384 blood samples, 334 (87%) were analyzed using the broad scope LC-TOF/MS postmortem protocol described previously, as opposed to directed testing by LC-QQQ-MS for only the analyte of interest. Of the 334 cases containing full drug screening, 224 blood samples (67%) also contained fentanyl. Fentanyl blood concentrations in these polydrug cases ranged from 0.28 to 400 ng/mL, with mean and median concentrations of 21 and 11 ng/mL, respectively. Opiates and/or opioids (including fentanyl) were reported in 255 cases (76%) where an NSO was present. Methamphetamine and/or amphetamine, cocaine and/or benzoylecgonine (BZE), and cannabinoids were identified in 33%, 20%, and 29% of the cases, respectively, further underscoring the complex polydrug nature of these NSO death investigations. Designer benzodiazepines were also routinely encountered with NSOs, including etizolam, clonazolam and its metabolite 8-aminoclonazolam, bromazolam, phenazepam, and flualprazolam. Interestingly, flualprazolam was reported in 49% (n = 71) of isotonitazene cases. This could be attributed to peak positivity of flualprazolam coinciding with peak positivity of isotonitazene; however, there is also a report confirming the 2 drugs present together (a phenomenon increasingly called "benzo dope") in a powder material associated with a death investigation from the Midwest.[90]

Select cases are further detailed based on the NSO being a primary driver of toxicity and in some cases being reported as the cause of death. Table 3 contains demographics, case history, and additional toxicological findings. These 20 cases include both individuals who presented to the hospital after suspected overdoses who ultimately were unable to be resuscitated as well as decedents who were found unresponsive. Drug paraphernalia was commonly found, including descriptions of white powders and unknown pills. Autopsy findings, when available, commonly listed edematous organs. Cardiovascular disease was also noted in a number of individuals, which may limit an individual's physiological reserve and potentially putting them at more risk for the toxic effects of opioids.[122]

TABLE 1. Analytical Characteristics of Novel Synthetic Opioids

Analyte Name	Molecular Formula	Protonated Mass, Da	Retention Time, min
2-Methyl AP-237	$C_{18}H_{26}N_2O$	287.2118	5.196
AP-238	$C_{18}H_{26}N_2O$	287.2118	5.83
Brorphine	$C_{20}H_{22}BrN_3O$	400.1019	5.220
Etodesnitazene	$C_{22}H_{29}N_3O$	352.2383	5.024
Isotonitazene/protonitazene	$C_{23}H_{30}N_4O_3$	411.2391	5.683
Metonitazene	$C_{21}H_{26}N_4O_3$	383.2078	4.958
N-pyrrolidino etonitazene	$C_{23}H_{26}N_4O_3$	395.2078	5.152

TABLE 2. Concentrations (in Nanograms per Milliliter) of Novel Synthetic Opioids Reported in Postmortem Investigations

Drug	N	Average ± STD	Median	Range
Isotonitazene	144	2.8 ± 9.2	0.93	0.11–99
Metonitazene	122	5.1 ± 7.0	2.6	0.5–50
Brorphine	91	3.9 ± 12	1.3	0.27–110
N-pyrrolidino etonitazene	13	4.4 ± 6.2	2.5	0.64–25
Protonitazene	6	239 ± 519	4.0	1.3–1400
Etodesnitazene	3			1.8, 30, 69
2-Methyl AP-237	3			11,100, 320
AP-238	2			87, 270

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TABLE 3. Selected Case Histories With Limited Additional Findings

Case	Case Synopsis	State	Collection Date	Sample Source	NSO, ng/mL	Additional Findings, ng/mL	COD
1	27 y/o M was discovered deceased by his ex-girlfriend and his roommate after not being able to make contact with him. Drug paraphernalia found on scene including several vials filled with unknown powders, orange pills, and marijuana.	WA	Jan 2020	Femoral blood	Isotonitazene 1.5	Delta-9 THC 7.6, THCC 81, 11-hydroxy 11-hydroxy THC 3.0, venlafaxine 92, *O*-desmethylvenlafaxine 580	Acute venlafaxine and isotonitazene intoxication
2	83 y/o M was found unresponsive in hotel room. Decedent had a history of providing drugs in exchange for sex and checked into the hotel with 2 female companions the previous day. The females found the decedent unresponsive in the bathroom. Drugs (heroin and fentanyl) were located in one of the female's purses. Vomit was observed around the decedent's mouth.	FL	Feb 2020	Iliac blood	Isotonitazene 1.6	Donepezil 7.8	Not provided
3	A 59 y/o M with a history of substance abuse and a recent heroin and cocaine overdose was found unresponsive in residence. Autopsy findings included cerebral edema, pulmonary congestion and edema, in addition to several cardiovascular related pathological findings.	IL	April 2020	Peripheral blood	Isotonitazene 0.68	No other findings	Isotonitazene intoxication; significant contributing factor of coronary atherosclerosis and dilated cardiomyopathy
4	33 y/o F with history of heroin and methamphetamine use was found unresponsive at friend's house supine on the floor. Partially digested food was within her mouth and on her lips. Autopsy findings included moderate pulmonary congestion.	GA	August 2020	Iliac blood	Brorphine 1.1	EtOH 83 mg/dL	Combined brorphine and ethanol toxicity
5	26 y/o M found unresponsive in residence; EMS responded and transported individual to hospital. ER interventions included CPR but was pronounced deceased approximately 45 min after EMS was contacted. No toxicology was drawn in ER. Mucus was noted emanating from mouth and nose and a white powder was located by the decedent. Autopsy findings included cerebral and pulmonary edema.	IL	September 2020	Peripheral blood	Brorphine 0.56	BZE 120	Brorphine and cocaine intoxication
6	59 y/o F found deceased outside in front of unoccupied building. Autopsy findings included mild pulmonary edema and atherosclerotic/hypertensive cardiovascular disease. No findings during autopsy of hypothermia.	NV	Jan 2021	Peripheral blood	Brorphine 12	EtOH 144 mg/dL	Brorphine and ethanol toxicity

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TABLE 3. *(Continued)*

Case	Case Synopsis	State	Collection Date	Sample Source	NSO, ng/mL	Additional Findings, ng/mL	COD
7	43 y/o M decedent had presented himself to a hospital before death after an apparent accidental overdose of a "30-mg Percocet"; urine toxicology screen was positive for benzos and marijuana. He was discharged after approximately 5 h. Autopsy findings included cerebral edema (brain weight 1495 g), pulmonary congestion and edema, with right and left lung weights 957 and 1092 g.	IL	January 2021	Femoral blood	Isotonitazene 0.71 Brorphine 3.6	Delta-9 THC 6.7, diphenhydramine 530	Combined drug toxicity
8	52 y/o M found unresponsive in vehicle. Extensive underlying cardiac and pulmonary pathological conditions.	FL	January 2021	Iliac blood	*N*-pyrrolidino etonitazene 8.3	No additional findings	Natural
9	28 y/o M with history of substance abuse was found unresponsive in bed. Drug paraphernalia was found next to the decedent included a spoon with residue, a yellow metal plate with residue, a pipe, a grinder, and a bag of white powdered substance. A pink foam cone was noted emerging from the subject's mouth. Individual was scheduled for back surgery and had been prescribed pain medication. Individual was prescribed fluoxetine and alprazolam. Decedent also tested positive for COVID-19. The white powdered substance was chemically determined to be AP-238.	IL	January 2021	Peripheral blood	AP-238 270	Delta-9 THC 16, THCC 110, 11-hydroxy delta-9 THC 6.8, acetaminophen 18 μg/mL	Probable drug toxicity (AP-238 and other possible novel substances)
10	41 y/o M was found face down, unresponsive in a shed with no signs of trauma. Drug paraphernalia located on scene included marijuana, needles, and empty baggies. "Synthetic heroin" was the known drug choice for the decedent and he would order it online. Autopsy findings included pulmonary congestion and edema, cerebral edema, and aspiration of gastric contents.	FL	February 2021	Iliac blood	AP-238 87	Methadone 680, EDDP 62, δ-9 THC 0.87, THCC 18, 11-hydroxy δ-9 THC 1.0, memantine 590	Combined methadone and AP-238 toxicity

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TABLE 3. *(Continued)*

Case	Case Synopsis	State	Collection Date	Sample Source	NSO, ng/mL	Additional Findings, ng/mL	COD
11	49 y/o with history of substance and alcohol abuse was discovered unresponsive outside residence and EMS was contacted. He was transferred to a hospital where resuscitation efforts were discontinued after roughly 50 min. Autopsy findings included pulmonary edema in addition to hypertensive cardiovascular disease. Heavy lungs were noted; right lung weighed 1207 g and left lung weighed 1013 g.	IL	March 2021	Femoral blood	Metonitazene 0.96	EtOH 302 mg/dL	Metonitazene and ethanol toxicity
12	20 y/o M with history of "Molly" and alprazolam use found deceased in bed by girlfriend. EMS responded but victim was pronounced on scene. He was last seen alive 3 h earlier and not have any current prescription medications. Drug chemistry on seized materials confirmed 2-methyl AP-237, clonazolam, and fluoromethylphenidate in different tablet forms as well as psilocin/psilocybin mushrooms. Autopsy findings included biventricular hypertrophy and dilatation (heart 530 g), hepatosplenomegaly and pulmonary congestion/edema (1760 g combined).	SC	March 2021	Iliac blood	2-Methyl AP-237 320	8-aminoclonazolam 22, 7-aminoclonazepam 7.6	2-Methyl AP-237 and 8-aminoclonazolam (clonazolam) toxicity
13	F with history of drug abuse was found unresponsive, blue in color, and cold to the touch in residence after IV use of "gray heroin." Drug paraphernalia was found on scene. Pulmonary edema was noted at autopsy.	IL	March 2021	Peripheral blood	Metonitazene 7.1	Delta-9 THC 2.1	Metonitazene toxicity
14	53 y/o M was found unresponsive in a hotel room. Drug paraphernalia, including needles and baggies of unknown white powders, were located on scene. Autopsy findings included mild pulmonary congestion and edema. The lungs weighed 573 (right) and 481 g (left). Additional pathological findings included hypertensive and atherosclerotic cardiovascular disease.	IL	April 2021	IVC blood	Metonitazene 1.2	Diphenhydramine 150, gabapentin 17 μg/mL	Metonitazene toxicity with contributing factor hypertensive and atherosclerotic cardiovascular disease

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TABLE 3. *(Continued)*

Case	Case Synopsis	State	Collection Date	Sample Source	NSO, ng/mL	Additional Findings, ng/mL	COD
15	32 y/o F with history of IV opiate and methamphetamine use, prescription drug abuse, and asthma found unresponsive in a parked vehicle. Heroin was reportedly found on scene. She was transferred to a hospital and diagnosed with an anoxic brain injury with lactic acidosis and status epilepticus. She never regained consciousness and was pronounced deceased 5 d later. Admission urine was negative under hospital screening.	GA	April 2021	Hospital blood	Metonitazene 7.0	No additional findings	Complications of metonitazene intoxication
16	A 22 y/o M was found deceased in his dorm room. Two scales, one with a brown residue and the other with a white residue, were located in the room in addition to small baggies, liquid syringes, vape and a number of substances, including modafinil, melatonin, valerian root, and propylene glycol.	IA	May 2021	Femoral blood	Etodesnitazene 30	3-Fluorophenmetrazine, mitragynine 310, etizolam 12, alpha-hydroxyetizolam 14, amphetamine 370, gabapentin 6.7 μg/mL, sertraline 1000, desmethylsertraline 1200, olanzapine 38, BZE 140, EtOH 12 mg/dL	Mixed drug intoxication
17	35 y/o M with history of drug and alcohol abuse and compromised cardiovascular function transferred to hospital in cardiac arrest and diagnosed with anoxic brain injury. Decedent died 3 d later in the hospital.	IL	May 2021	Hospital blood	Metonitazene 1.8	EtOH 167 mg/dL	Hypoxic ischemic encephalopathy from metonitazene and alcohol intoxication with significant contributing factor of ischemic hypertensive cardiovascular disease
18	19 y/o M was found unresponsive by a friend. Immediate history included marijuana use. Five unmarked tablets found on scene. Drug chemistry indicated presence of isotonitazene and oxycodone.	Ontario	May 2021	Femoral blood	Isotonitazene 0.4	Delta-9 THC 2.1, THCC 10	Isotonitazene toxicity
19	41 y/o M with history of substance use and recent incarceration was found deceased in a hotel room. Immediate history of retrieving illicit drugs with girlfriend from unknown source. Girlfriend left hotel room to purchase something from a vending machine, and found the decedent unresponsive upon her return, lying on his back with his fists clenched at his chest and cell phone in his hands. Girlfriend admitted to engaging in cocaine use just before decedent being found unresponsive. A small unspecified pill was found located on a small table.	LA	June 2021	Cardiac blood	Protonitazene 1400 Etodesnitazene 1.8	Cocaine 1500, BZE 3100, cocaethylene 260, delta-9 THC 9.0, THCC 6.8, doxepin 110, EtOH 47 mg/dL	Mixed drug toxicity

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TABLE 3. *(Continued)*

Case	Case Synopsis	State	Collection Date	Sample Source	NSO, ng/mL	Additional Findings, ng/mL	COD
20	61 y/o M found unresponsive by family. Substance tested positive for fentanyl in possession.	WI	July 2021	Hospital blood	Metonitazene 1.1	EtOH 228 mg/dL	Not provided

EMS, emergency medical services; EtOH, ethanol; F, female; IV, intravenous; IVC, inferior vena cava; M, male; EDDP, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine; THC, tetrahydrocannabinol; THCC, 11-nor-δ-9-tetrahydrocannabinol-9-carboxylic acid; ER, emergency room; y/o, years old.

Isotonitazene

Isotonitazene was quantitatively confirmed in 144 blood samples (43%) collected from medicolegal death investigations and 2 DUI investigations involving NSOs during this study period. Although quantitative testing capabilities were not available until January 2020 from the reporting laboratory, the earliest collection date for a postmortem blood sample was April 2019. In total, 7 blood samples from cases collected in 2019 were confirmed to contain isotonitazene after the availability of quantitative testing by the laboratory. In 2 postmortem cases in which no other additional findings were detected in toxicology, isotonitazene was reported at concentrations of 0.68 and 3.2 ng/mL in blood.

One hundred seventeen cases (87%) were collected or submitted before June 2020, the month in which the DEA announced intent to schedule isotonitazene (final ruling occurred in August 2020).[92] After this scheduling action, detections of isotonitazene dropped off significantly (Fig. 2), although cases continue to be sporadically reported. In total, the postmortem cases were received from 22 states. Wisconsin accounted for the highest number of isotonitazene confirmations (n = 28), followed by Illinois (n = 24), Florida (n = 16), Tennessee (n = 11), and Minnesota (n = 10). In addition to the US, the Canadian provinces of Quebec, Ontario, and Newfoundland also accounted for cases involving isotonitazene.

Brorphine

Brorphine was first reported by our laboratory in August 2020, shortly after the scheduling of isotonitazene and after the laboratory expanded its scope of testing to include brorphine. The earliest collected and submitted specimens were from July 2020. Cases involving brorphine peaked in September 2020 and eventually dropped to less than 5 per month by February 2021. Notice of intent to schedule brorphine was issued in December 2020.[106] In total, 93 blood samples have been reported to contain brorphine thus far; 61% of which were reported by December 2020. Only 16 cases were collected and reported after February 2021. In one postmortem blood sample where only benzoylecgonine was reported, brorphine was reported at 0.56 ng/mL. Brorphine was reported at 1.1 and 12 ng/mL in additional postmortem blood cases where only ethanol was additionally reported.

Brorphine has been reported in death investigation cases from both the US and Canada (British Columbia), as well as 2 DUI investigations. Wisconsin and Illinois accounted for 22 and 21 cases each, followed by Minnesota (n = 17), Georgia (n = 7), and West Virginia (n = 5). Twelve additional states report less than 5 cases each, spanning different parts of the country and included Tennessee, Florida, Colorado, Nevada, and New York.

Metonitazene

Metonitazene appeared next after a drop in brorphine positivity subsequent to DEA's notice of intent to schedule brorphine in December 2020. Metonitazene was first reported by our laboratory in April 2021 after the development of a quantitative testing method. The earliest collected samples containing metonitazene were from February 2021. As of December 2021, metonitazene continues to be detected and confirmed in casework. By the end

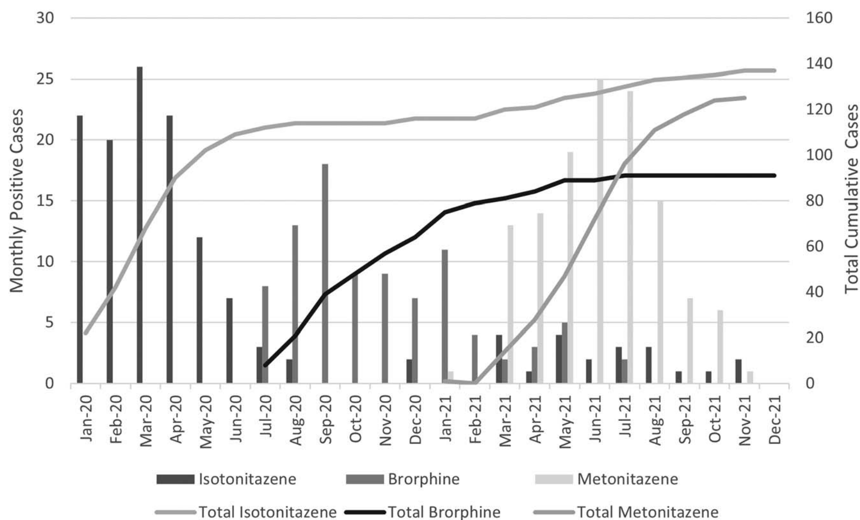

FIGURE 2. Blood confirmations of isotonitazene, brorphine, and metonitazene after successive emergence and proliferation due to individual DEA drug scheduling actions.

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of December 2021, 122 postmortem bloods were reported positive for metonitazene in addition to 4 DUI cases. The temporal trend involving the shift from isotonitazene to brorphine to metonitazene is illustrated in Figure 2. In 2 postmortem cases in which metonitazene was the only toxicological finding, it was reported in blood at 5.7 and 7.0 ng/mL. Three other postmortem cases only included ethanol in addition; these blood concentrations included 0.96, 1.1, and 1.8 ng/mL.

Similar to its 2 predecessors, metonitazene has been detected in 18 US states and British Columbia. Illinois (n = 26), Wisconsin (n = 22), and Kentucky (n = 21) accounted for the highest number of cases, followed by Tennessee (n = 17), Iowa (n = 13), and Minnesota (n = 8).

AP Series

To date, 5 cases involving cinnamylpiperazines have been reported. AP-238 was confirmed in 2 postmortem cases from Illinois and Florida; one case was collected in January 2021 and the other was collected in February 2021. 2-Methyl AP-237 was confirmed in a case from South Carolina from March 2021, a second case from Wisconsin collected in April 2021, and a third postmortem case from Pennsylvania collected in November 2021.

Additional Nitazene Analogs

N-pyrrolidino etonitazene has primarily been reported in cases originating from West Virginia (n = 5), British Columbia (n = 3), Florida (n = 2), and one each from New Jersey, Kentucky, and Minnesota. The first reported case was originally collected in January 2021; 6 cases were collected in September, illustrating the increase in prevalence over time. Protonitazene was first reported in a case from Texas collected in April 2021, followed by cases from Iowa, New Jersey, Louisiana, Missouri, and British Columbia. Etodesnitazene was first reported in a case from Iowa collected in May 2021, with subsequent cases reported from Louisiana, West Virginia, and Iowa (n = 1). The singular case from Louisiana contained both protonitazene and etodesnitazene.

DISCUSSION

The emergence, proliferation, and positivity of a new synthetic drug is greatly influenced by a number of factors, including temporal changes in response to drug scheduling actions, market forces, geographical trends, and varying surveillance capabilities. Unabated by scheduling of fentanyl-related substances, next-generation NSOs continue to appear on the drug market and have been confirmed to be involved in multiple drug overdoses and deaths.

Isotonitazene was the first nitazene analog to emerge and its lifespan has since been characterized, in addition to its successor brorphine. The total lifespan of both of these substances was roughly 12 months, with a peak range of positivity for only approximately 6 months.[123] Metonitazene is still experiencing sustained positivity as of December 2021, so its longevity cannot be truly assessed. Metonitazene was recently listed under DEA intent for scheduling 7 different nitazene compounds.[120] The lifespan of metonitazene is hypothesized to follow that of isotonitazene and brorphine once it is controlled but is it too soon to tell. *N*-pyrrolidino etonitazene has experienced increased positivity over the last quarter of 2021 but falls under the recent scheduling measure. Other encountered nitazene analogs and other subclasses of NSOs are experiencing scattered positivity, and as such, we continue to monitor these substances. Based on prior experience, it is likely that now that metonitazene is scheduled, one of the other nitazene analogs with comparable potency will then increase in positivity to fill the void that metonitazene will leave behind. It is also possible that the NSO market will eventually shift to a new class of opioid agonists or a new analog from a different already known subclass. Monitoring online social media and drug use forums, such as Reddit threads, may help predict (or at least be prepared for) the next NSO market shift.[124] It is hypothesized that the cinnamylpiperazines are not experiencing increased or sustained popularity because of their relatively lower potencies compared with other available NSOs and the consequences that could have on drug product amounts, pricing, availability, the created "high" produced by the drug, and/or user preference patterns.

Novel synthetic opioids are most commonly encountered as contaminants or concomitants in the fentanyl/heroin opioid supply but may also be found by themselves. Common drug preparations include pills (eg, counterfeit oxycodone), powders (eg, heroin, pure drug material), nasal sprays, etc. Novel synthetic opioids can be purchased through the Internet, which can lead to introduction of the drugs into the larger supply or purchasing for personal use. When NSOs are reported in toxicology samples along with fentanyl and/or heroin, it is often assumed that the NSO is mixed with the dominant drug or contaminating the illicit opioid supply; however, one should not rule out concurrent or concomitant use in this era of polydrug use. Unknowing ingestion of NSOs certainly poses heightened risks of overdosing to end users, although naloxone has been reported to be effective for many of these newer NSOs, but potentially requiring additional doses. In the US, greatest positivity for NSOs centers around the same states, predominantly in the Great Lakes and Appalachian regions, with many of these cases also reporting additional illicit opioids. Wisconsin, Illinois, Minnesota, and Iowa accounted for 51% of cases containing NSOs. Kentucky, Tennessee, and West Virginia accounted for another 19%, followed by Georgia, Louisiana, and Florida for 11% of cases. In total, 31 different US states and 4 Canadian provinces submitted cases for analysis that confirmed positive for at least one of the included NSOs. There is certainly a regional component to NPS trends, including those observed with these novel substances, but positivity is undoubtedly underestimated due to variable scopes and testing strategies by toxicology laboratories.[125]

The continued trend of polydrug use remains a challenge for medical examiners and toxicologists when attempting to assess toxicity of a new substances, especially NSOs. This challenge is in part due to a lack of scientific data involving polydrug cases and polydrug cases where complete expanded toxicology testing was conducted and all results are reported or considered. As observed in this case series, fentanyl and other opioids, methamphetamine and amphetamine, cocaine, cannabis, and benzodiazepines (both prescription and NPS) were all encountered to varying degrees in combination with NSOs. In some cases, multiple NSOs included in the scope of this work were detected, and the shift in detected combinations reflects the overall changes in positivity in response to scheduling actions. For example, isotonitazene and brorphine were found in combination in a postmortem blood collected in August 2020. One year later, a postmortem blood sample was reported to include a combination of protonitazene and *N*-pyrrolidino etonitazene. Only 5 cases (1.8%) who underwent comprehensive toxicology testing reported no other findings with the NSO, with an additional 5 cases (2%) reporting only ethanol in addition to the NSO. The purpose of this selected case series is to help share fatal overdose data in which an NSO was ruled or suspected to be the primary driver of toxicity. In addition, this report shares some of the first reported quantitative detections of protonitazene and etodesnitazene in toxicological casework.[126]

The increasing expansion and diversity of substances in the NSO class of NPS continue to challenge toxicology laboratories and forensic scientists. Every time a new drug emerges, both screening and confirmation workflows must be updated and

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verified or validated. These time-consuming processes rely on the availability of certified reference material, staffing, scientist availability, and appropriate instrumentation. These are all challenges faced by large laboratories with dedicated resources, let alone hospital laboratories with a much smaller testing scope that may miss an NSO entirely in their screening, as was the situation in case 10. Analytical testing for NSOs must be highly sensitive (excluding the cinnamylpiperazines) and highly specific, because many of the reported concentrations are sub 1 ng/mL and testing is being performed on postmortem blood samples. One protonitazene case contained 1400 ng/mL and was considered an outlier compared with the lower concentrations exhibited in most cases. Furthermore, the presence of isomeric pairs (eg, isotonitazene and protonitazene, AP-238, and 2-methyl AP-237) complicates analytical testing, requiring techniques that can appropriately separate and distinguish these NSO pairs for accurate reporting.

The findings and temporal and geographic trends reported in this communication reflect only those cases submitted to this laboratory for testing and, therefore, do not reflect the overall scale of use or adverse outcomes of these drugs across the US. In addition, we encountered several cases that were positive by LC-TOF/MS screening, but at the direction of the agency submitting the case, were not forwarded for confirmation and quantitation and were, therefore, not included in this report. This is especially true in cases in which there were sufficient additional drugs present to account for a toxicological cause of death. Furthermore, confirmatory testing for cases submitted in late 2021 may not have completed toxicological testing within the reporting period, therefore potentially skewing the positivity for Q4 2021. The trends reported herein are not a full characterization of positivity in the US per substance; however, they represent the largest and most complete dataset available in the US currently. The variability in testing and resource strain faced by many medical examiner and coroner offices across the US results in an underreporting of NSOs, which will impact the numbers but should not affect the generalized trends observed.

CONCLUSIONS

Novel psychoactive substance markets have always been dynamic, with new substances constantly displacing "old" substances, and newly controlled drugs, or substances unpopular among drug users. The classwide ban on fentanyl-related substances (otherwise known as core structure scheduling) by the DEA in early 2018, as well as other international controls, seems to have been an effective strategy for decreasing prevalence of fentanyl analogs but has resulted in increased variety (and potency) among the NSO subclass.[127,128] In all, an opportunity for proliferation of nonfentanyl-related subclasses of opioid agonists has begun and continues to be dynamic.

The shift away from fentanyl analogs toward next-generation NSOs was not necessarily unexpected by the drug-monitoring community, especially because laboratories have observed many shifts among NPS classes since the late 2000s. Improved surveillance detection capabilities, analytical workflows, and data sharing have resulted in earlier signals, detections, and reporting. Because of the collaborative efforts between drug surveillance institutions, public health agencies, toxicology laboratories, drug chemists, regulatory and law enforcement agencies, pharmacological characterization efforts, death investigators, and policy experts, the longevity of individual NSO compounds seems to be decreasing, now frequently less than a year of peak popularity; however, this decrease may make the work of these individuals more challenging as new, more potent NSOs emerge. New opioid agonists continue to pose a threat to public health and safety, and medical examiners and coroners are seeing the effects of the dangers in the form of fatal overdoses. This case series highlights the continued need for the death investigation community to be vigilant for emerging NSOs.

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